to "different reactivity, binding affinity, mechanism, stability, polarity, bioavailability, efficacy, solubility, and modes of action" as asserted on page 4 of the Restriction Requirement. In fact, Applicants note that the compounds of general formula (I) are nitroderivatives of drugs belonging to two specific therapeutic classes, which are non-steroidal anti-inflammatory drugs (NSAIDs) and diuretics. The NSAIDs class comprises radicals of subgroups IA to V Ac and VIA, and the diuretics class comprises structures of subgroups V Ad and V Ae. Further, among the NSAIDs class, the subgroups may be divided according to the therapeutic classification reported in THE MERCK INDEX 13th Ed. (attachment labeled as "Enclosure 1") into:

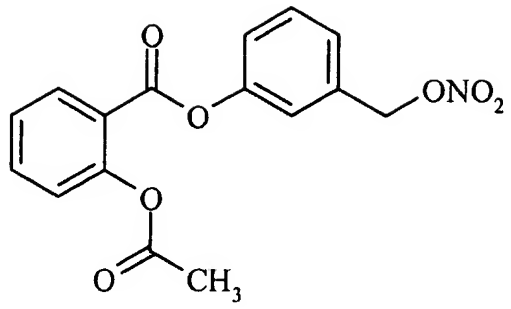
- arylpropionic acid derivatives which comprise "R" radicals of formulae: Group IIAa) formulae (II), (XXI), (IV), (VII), (XXXV), (VI), and (IX); Group IIAb) formulae (IIa), (XXX), and (XXXVI); and Group IIIA) formulae (II), (X), and (III);
- arylacetic acid derivatives which comprise "R" radicals of formulae: group IIAa) formulae (VIII) and (X); Group IIAb) formulae (XXXII), (XXXIII) and (XXXVII); and (IV);
- aminoarylcarboxylic acid derivatives which comprise "R" radicals of formulae: (V Aa1), (V Aa2), (V Aa3), (V Aa4), and (V Ab1);
- salicyclic acid derivatives which comprise "R" radicals of formulae: Group VIA) formula (Ia); and
- NSAIDs having a sulfonamide function which comprise "R" radicals of formulae: (V Ac1), (V Ac2), (V Ac3), (V Ac4), and (V Ac5).

Moreover, as demonstrated by pages 63-66 titled "Monographs on Drugs and Ancillary Substances: Analgesics Anti-inflammatory Drugs and Antipryetics" (attachment labeled as "Enclosure 2"), the class of NSAIDs are a known group of compounds that have analgesic, anti-inflammatory, and antipyretic properties. NSAIDs are the inhibitors of the enzyme cyclooxygenase and thus inhibit the biosynthesis of prostaglandins and thromboxanes from arachidonic acid. Further, this class of compounds generally has the same adverse effects, i.e., gastrointestinal disturbances, the same interactions with other drugs, and the same use and administration as reported pages 63-66 titled "Monographs on Drugs and Ancillary Substances: Analgesics Anti-inflammatory Drugs and Antipryetics" (attached as Enclosure 2). Therefore, although the NSAIDs have different chemical structures, they have the same mechanism and modes of action, comparable efficacy and similar side effects.

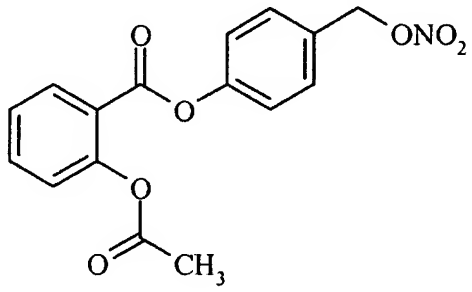
Accordingly, Applicants respectfully request withdrawal of the secondary restriction requirement between of a single formula of subgroups IA-VIA, the formulae of subgroups I-VAc and the formulae of subgroup VIA are not unconnected in "design, operation, and effect" (emphasis added). MPEP §§ 802.01 and 806.06.

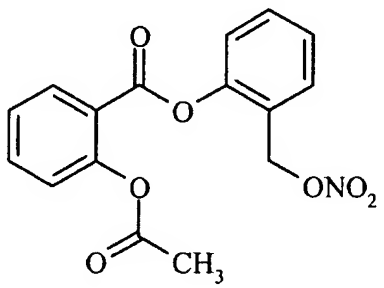
For at least the above reasons, Applicants respectfully request reconsideration and withdrawal of the restriction requirement.

In response to the Election of Species Requirement, Applicants hereby provisionally elect the 3-(nitroxymethyl)phenyl ester of aspirin of present claim 5 for prosecution on the merits **with traverse**, which has the following formula:



However, as 3-(nitroxymethyl)phenyl ester of aspirin is an isomer of the other two nitroxymethyl phenyl esters of aspirin of claim 5, illustrated below, Applicants respectfully submit that an election all three compounds should be allowed in response to the Election of Species Requirement.





In view of the Applicant's above elections, the Applicants respectfully submit that the Restriction Requirement and the Election of Species Requirement have been satisfied. The Applicants submit that claims 1, 2, and 4-6 read on the elected species. Accordingly, the Applicants respectfully request examination of the claims on the merits.

In the event this paper is not considered to be timely filed, Applicant hereby petitions for an appropriate extension of time. The fee for this extension may be charged to our Deposit Account No. 01-2300, referring to Attorney Docket No. **026220-00039**. Please charge any fee deficiency or credit any overpayment to Deposit Account No. 01-2300, referencing Attorney Docket No. **026220-00039**.

Respectfully submitted,

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Enclosures: References (2)

ENCLOSURE 1

ANTIHYPERTHYROID (*continued*)
Sodium Perchlorate, *8726*
Thibenzazoline, *9383*
Thiobarbital, *9393*
2-Thiouracil, *9442*

ANTIHYPOTENSIVE
Amezinium Methyl Sulfate, *392*
Angiotensin Amide *see 654*
Dopamine, *3455*
Dimetofrine, *3291*
Etifelmin, *3895*
Etilefrin, *3897*
Gepefrine, *4413*
Metaraminol, *5957*
Methoxamine, *6017*
Midodrine, *6208*
Norepinephrine, *6727*
Pholedrine, *7415*
Synephrine, *9104*

ANTIHYPOTHYROID
Thyroid, *9487*
Liothyronine, *5532*
Thyroidin, *9488*
Thyroxine, *9491*
Tiratricol, *9539*
TSH, *9870*

ANTI-INFECTIVE *see Antiseptic/Disinfectant*

ANTI-INFLAMMATORY (GASTROINTESTINAL)
Balsalazide, *947*
Mesalamine, *5931*
Olsalazine, *6911*
Sulfasalazine, *9028*

ANTI-INFLAMMATORY (NONSTEROIDAL) *see also Antiarthritic/Antirheumatic*

Aminoarylcarboxylic Acid Derivatives
Enfenamic Acid, *3614*
Etofenamate, *3907*
Flufenamic Acid, *4158*
Isonixin, *5211*
Meclofenamic Acid, *5802*
Mefenamic Acid, *5821*
Niflumic Acid, *6557*
Talniflumate, *9134*
Terofenamate, *9244*
Tolfenamic Acid, *9590*

Arylacetic Acid Derivatives
Aceclofenac, *22*
Acemetacin, *28*
Alclofenac, *218*
Amfenac, *393*
Amtolmetin Guacil, *600*
Bromfenac, *1374*
Bufexamac, *1461*
Cinmetacin, *2316*
Clopirac, *2423*
Diclofenac, *3108*
Etodolac, *3905*
Felbinac, *3979*
Fenclozic Acid, *3996*
Fentiazac, *4031*
Glucametacin, *4461*
Ibufenac, *4905*
Indomethacin, *4990*
Isoxepac, *5259*
Lonazolac, *5587*
Metiazinic Acid, *6160*
Mofezolac, *6254*
Oxametacine, *6985*
Pirazolac, *7571*
Proglumetacin, *7865*
Sulindac, *9072*
Tiaramide, *9500*
Tolmetin, *9595*
Tropesin, *9848*
Zomepirac, *10243*

Arylbutyric Acid Derivatives
Bumadizon, *1470*
Butibufen, *1521*
Fenbufen, *3990*
Xenbucin, *10128*

Arylcarboxylic Acids
Clidanac, *2374*
Ketorolac, *5324*
Tinoridine, *9526*

Arylpropionic Acid Derivatives
Alminoprofen, *297*
Benoxaprofen, *1044*
Bermoprofen, *1162*
Carprofen, *1876*
Fenoprofen, *4007*
Flunoxaprofen, *4174*
Flurbiprofen, *4225*
Ibuprofen, *4906*
Ibuproxam, *4907*
Indoprofen, *4991*
Ketoprofen, *5322*
Loxoprofen, *5611*
Naproxen, *6443*
Oxaprozin, *6993*
Piketoprofen, *7503*
Pirprofen, *7591*
Pranoprofen, *7796*
Protizinic Acid, *7983*
Suprofen, *9095*
Tiaprofenic Acid, *9498*
Ximoprofen, *10133*
Zaltoprofen, *10166*

Pyrazoles
Difenamizole, *3159*
Epirizole, *3653*

Pyrazolones
Apazone, *733*
Benzpiperylon, *1120*
Feprazone, *4040*
Mofebutazone, *6252*
Morazone, *6290*
Oxyphenbutazone, *7041*
Phenylbutazone, *7361*
Pipebuzone, *7538*
Propyphenazone, *7963*
Ramifenazone, *8193*
Suxibuzone, *9100*
Thiazolinobutazone, *9379*

Salicylic Acid Derivatives
Acetaminosalol, *49*
Aspirin, *856*
Balsalazide, *947*
Benorylate, *1043*
Calcium Acetylsalicylate, *1646*
Diflunisal, *3170*
Fendosal, *3998*
Gentisic Acid, *4409*
Glycol Salicylate, *4512*
Imidazole Salicylate, *4936*
Lysine Acetylsalicylate, *5657*
Mesalamine, *5931*
Morpholine Salicylate *see 6303*
1-Naphthyl Salicylate, *6440*
Olsalazine, *6911*
Parsalmide, *7117*
Phenyl Acetylsalicylate, *7354*
Phenyl Salicylate, *7394*
Salacetamide, *8398*
Salicylamide *O*-Acetic Acid, *8408*
Salicylsulfuric Acid, *8413*
Salsalate, *8418*
Sodium Salicylate *see 8411*
Sulfasalazine, *9028*

Thiazinecarboxamides
Ampiroxicam, *592*
Droxicam, *3491*
Isoxicam, *5260*
Lornoxicam, *5603*
Piroxicam, *7589*
Tenoxicam, *9225*

Others
ε-Acetamidocaproic Acid, *46*
S-Adenosylmethionine, *157*
3-Amino-4-hydroxybutyric Acid, *442*
Bendazac, *1032*
Benzydamine, *1124*
α-Bisabolol, *1241*
Bucolome, *1451*
Celecoxib, *1968*
Difenpiramide, *3762*
Ditazol, *3403*
Emorfazone, *3594*
Etanercept, *3747*
Fepradinol, *4039*
Guaiazulene, *4570*
Infliximab, *4995*
Interleukin-10, *5020*
Lexipafant, *5493*
Nabumetone, *6369*
Nimesulide, *6576*
Oxaceprol, *6971*
Paranyline, *7101*
Perisoxal, *7254*
Proquazone, *7965*
Rofecoxib, *8330*
Superoxide Dismutase, *9092*
Tenidap, *9221*

ANTI-INFLAMMATORY (STEROIDAL) *see Glucocorticoid*

ANTILEPROTIC *see Antibacterial (Leprostatic)*

ANTILEUKEMIC *see Antineoplastic*

ANTILIPEMIC *see Antihyperlipoproteinemic*

ANTILIPIDEMIC *see Antihyperlipoproteinemic*

ENCLOSURE 2

Part I

Monographs on Drugs and Ancillary Substances

Analgesics Anti-inflammatory Drugs and Antipyretics

The compounds described in this chapter are used mainly in the relief of pain, inflammation and, sometimes, fever. They can be grouped broadly into one of the categories briefly described below.

Aspirin and other Salicylates

Aspirin and other salicylates have analgesic, anti-inflammatory, and antipyretic properties. Like other NSAIDs (see below) they are inhibitors of the enzyme cyclo-oxygenase; however, aspirin (though not the non-acetylated salicylates) irreversibly acetylates the enzyme whereas other NSAIDs compete with arachidonic acid for the active site. Salicylates are used for the relief of mild to moderate pain, minor febrile conditions, and for acute and chronic inflammatory disorders such as osteoarthritis, rheumatoid arthritis, juvenile idiopathic arthritis, and ankylosing spondylitis. Some salicylates are applied topically in rubefacient preparations for the relief of muscular and rheumatic pain. Aspirin also inhibits platelet aggregation and is used in cardiovascular disorders. Non-acetylated salicylates do not have antiplatelet activity.

For further discussion of the actions and uses of salicylates, see Aspirin, p.14.

Described in this chapter are
- Aloxiprin, p.13
- Aluminium Aspirin, p.13
- Ammonium Salicylate, p.14
- Amyl Salicylate, p.14
- Aspirin, p.14
- Bornyl Salicylate, p.20
- Carbasalate Calcium, p.23
- Choline Magnesium Trisalicylate, p.24
- Choline Salicylate, p.24
- Diethylamine Salicylate, p.32
- Diflunisal, p.32
- Ethenzamide, p.35
- Ethyl Salicylate, p.35
- Fosfosal, p.42
- Glycol Salicylate, p.42
- Imidazole Salicylate, p.44
- Lithium Salicylate, p.50
- Lysine Aspirin, p.50
- Magnesium Salicylate, p.50
- Methyl Butetisalicylate, p.55
- Methyl Salicylate, p.55
- Morpholine Salicylate, p.59
- Picolamine Salicylate, p.78
- Salamidacetic Acid, p.81
- Salicylamide, p.82
- Salix, p.82
- Salol, p.82
- Salsalate, p.82
- Sodium Salicylate, p.84
- Sodium Thiosalicylate, p.84
- Thurfyl Salicylate, p.88
- Trolamine Salicylate, p.90

Disease-modifying Antirheumatic Drugs

Disease-modifying antirheumatic drugs (DMARDs) have anti-inflammatory properties thought to be mediated, in some cases, by the inhibition of the release or activity of cytokines. They are used in the treatment of rheumatoid arthritis and juvenile idiopathic arthritis; some are also of benefit in psoriatic arthritis. Many DMARDs also possess other therapeutic properties and are use in a wide variety of non-rheumatic conditions. The DMARD gold is referred to below; DMARDs discussed in other chapters include the antimalarials chloroquine (p.432) and hydroxychloroquine (p.437), sulfasalazine (p.1251), penicillamine (p.1017), and the immunosuppressants azathioprine (p.509), ciclosporin (p.518), cyclophosphamide (p.527), etanercept (p.1608), infliximab (p.1228), leflunomide (p.549) and methotrexate (p.553).

Gold compounds. Gold compounds are used mainly for their anti-inflammatory effect in active progressive rheumatoid arthritis and progressive juvenile idiopathic arthritis; they may also be beneficial in psoriatic arthritis. The mechanism of action of gold compounds in rheumatic disorders is as yet unknown.

For further discussion of the actions and uses of gold compounds, see Sodium Aurothiomalate, p.82.

Described in this chapter are
- Auranofin, p.18
- Aurothioglucose, p.18
- Auriotioprol, p.19
- Sodium Aurothiomalate, p.82
- Sodium Aurotiosulfate, p.84

Nonsteroidal Anti-inflammatory Drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a group of unrelated organic acids that have analgesic, anti-inflammatory, and antipyretic properties (see p.63). NSAIDs are inhibitors of the enzyme cyclo-oxygenase, and so directly inhibit the biosynthesis of prostaglandins and thromboxanes from arachidonic acid (see p.1438). There are 2 forms of cyclo-oxygenase, COX-1, which is the constitutive form of the enzyme, and COX-2, which is the form induced in the presence of inflammation. Inhibition of COX-2 is therefore thought to be responsible for at least some of the analgesic, anti-inflammatory, and antipyretic properties of NSAIDs whereas inhibition of COX-1 is thought to produce some of their toxic effects, particularly those on the gastrointestinal tract. Most of the NSAIDs currently available for clinical use inhibit both COX-1 and COX-2, although selective COX-2 inhibitors such as celecoxib and rofecoxib are becoming available.

NSAIDs are used for the relief of mild to moderate pain, minor febrile conditions, and for acute and chronic inflammatory disorders such as osteoarthritis, rheumatoid arthritis, juvenile idiopathic arthritis, and ankylosing spondylitis. Indometacin and some other NSAIDs are used to close patent ductus arteriosus in premature neonates. Some NSAIDs are applied topically for the relief of muscular and rheumatic pain, and some are used in ophthalmic preparations for ocular inflammatory disorders. Aspirin (see above) is considered to be an NSAID, although it has other properties.

Described in this chapter are
- Aceclofenac, p.11
- Acemetacin, p.11
- Alclofenac, p.11
- Alminoprofen, p.13
- Aminophenazone, p.13
- Aminopropylone, p.13
- Ampiroxicam, p.14
- Amtolmetin Guacil, p.14
- Azapropazone, p.19
- Bendazac, p.19
- Benoxaprofen, p.20
- Benzydamine, p.20
- Beta-uminoprupionitrile, p.20
- Bromfenac, p.20
- Isonixin, p.47
- Kebuzone, p.47
- Ketoprofen, p.47
- Ketorolac, p.48
- Lonazolac, p.50
- Lornoxicam, p.50
- Loxoprofen, p.50
- Meclofenamate, p.51
- Mefenamic Acid, p.51
- Meloxicam, p.51
- Mofebutazone, p.55
- Mofezolac, p.56
- Morniflumate, p.56
- Nabumetone, p.59
- Bufexamac, p.20
- Bumadizone, p.20
- Butibufen Sodium, p.22
- Carprofen, p.23
- Celecoxib, p.24
- Clofexamide, p.25
- Clofezone, p.25
- Clonixin, p.25
- Diclofenac, p.30
- Dipyrone, p.34
- Droxicam, p.34
- Eltenac, p.34
- Epirizole, p.35
- Etodolac, p.35
- Etofenamate, p.35
- Felbinac, p.36
- Fenbufen, p.36
- Fenoprofen, p.36
- Fentiazac, p.40
- Feprudinol, p.40
- Feprazone, p.40
- Floctafenine, p.40
- Flufenamic Acid, p.41
- Flunixin, p.41
- Flunoxaprofen, p.41
- Flurbiprofen, p.41
- Furprofen, p.42
- Glafenine, p.42
- Glucametacin, p.42
- Ibuprofen, p.43
- Ibuproxam, p.44
- Indometacin, p.44
- Naproxen, p.60
- Nifenazone, p.62
- Niflumic Acid, p.62
- Nimesulide, p.62
- Oxaprozin, p.70
- Oxyphenbutazone, p.71
- Parecoxib, p.74
- Phenazone, p.77
- Phenylbutazone, p.78
- Piketoprofen, p.78
- Piroxicam, p.79
- Pranoprofen, p.80
- Proglumetacin, p.80
- Propyphenazone, p.80
- Proquazone, p.80
- Ramifenazone, p.80
- Rofecoxib, p.81
- Sulindac, p.85
- Suprofen, p.87
- Suxibuzone, p.87
- Tenidap, p.87
- Tenoxicam, p.87
- Tetridamine, p.87
- Tiaprofenic Acid, p.88
- Tiaramide, p.88
- Tinoridine, p.88
- Tolfenamic Acid, p.88
- Tolmetin, p.88
- Ufenamate, p.90
- Valdecoxib, p.90
- Vedaprofen, p.90
- Zaltoprofen, p.90

Opioid Analgesics

Opioid analgesics include the opium alkaloids morphin and codeine and their derivatives as well as synthetic substances with agonist, partial agonist, or mixed agonis and antagonist activity at opioid receptors (see p.66). Th term opiate analgesics refers only to those opioids derived from opium, or their semisynthetic congeners. The term narcotic analgesics has legal connotations and is nc longer used pharmacologically or clinically.

The majority of opioids are used as analgesics, and morphine is the standard against which all other opioid analgesics are compared. Opioids such as codeine or dextropropoxyphene are used in the treatment of less severe pain, and are often combined with non-opioid analgesics such as aspirin, other NSAIDs, or paracetamol. More potent opioids such as morphine are used in severe acute and chronic pain, including cancer pain. Some opioids such as codeine, morphine, and diamorphine are also used as antitussives, although the latter two are usually reserved for use in terminal lung disease. Some opioid analgesics such as fentanyl and its congeners are used mainly as adjuncts to anaesthesia; some of these may also be used in higher doses as the sole anaesthetic drug.

Some opioids are not used as analgesics and are described elsewhere; they include the antitussives dextromethorphan (p.1087) and pholcodine (p.1099), and the antidiarrhoeals diphenoxylate (p.1222) and loperamide (p.1231).

of up to 200 mg twice daily by mouth or rectally for inflammatory conditions, fever, and pain. Nimesulide betadex (nimesulide betacyclodextrin complex) has been used similarly.

◊ References.

1. Bennett A, *et al.* Nimesulide: a multifactorial therapeutic approach to the inflammatory process? a 7-year clinical experience. *Drugs* 1993; 46: (suppl 1): 1–283.
2. Davis R, Brogden RN. Nimesulide: an update of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy. *Drugs* 1994; 48: 431–54.
3. Senna GE, *et al.* Nimesulide in the treatment of patients intolerant of aspirin and other NSAIDs. *Drug Safety* 1996; 14: 94–103.
4. Vizzardi M, *et al.* Nimesulide beta cyclodextrin (nimesulide-betadex) versus nimesulide in the treatment of pain after arthroscopic surgery. *Curr Ther Res* 1998; 59: 162–71.
5. Bernareggi A. Clinical pharmacokinetics of nimesulide. *Clin Pharmacokinet* 1998; 35: 247–74.
6. Shah AA, *et al.* Selective inhibition of COX-2 in humans is associated with less gastrointestinal injury: a comparison of nimesulide and naproxen. *Gut* 2001; 48: 339–46.

Adverse effects. Although *thrombocytopenia* is a common feature in patients infected with HIV one group of workers considered that thrombocytopenia in one of their patients was related to the use of nimesulide.[1]

There has been a report[2] of a patient who developed *fulminant hepatic failure* after treatment with nimesulide.

Irreversible *end-stage renal failure* has been reported in a neonate born to a mother who received nimesulide as a tocolytic from the 26th to the 32nd week of pregnancy.[3] Others have also reported neonatal renal failure associated with nimesulide use.[4]

1. Pastieci MB, *et al.* Nimesulide, thrombocytopenic purpura, and human immunodeficiency virus (HIV) infection. *Ann Intern Med* 1990; 112: 233–4.
2. McCormick PA, *et al.* COX 2 inhibitor and fulminant hepatic failure. *Lancet* 1999; 353: 40–1.
3. Peruzzi L, *et al.* Neonatal end-stage renal failure associated with maternal ingestion of cyclo-oxygenase-type-2 selective inhibitor nimesulide as tocolytic. *Lancet* 1999; 354: 1615. Correction. *ibid.* 2000; 355: 238.
4. Balasubramaniam J. Nimesulide and neonatal renal failure. *Lancet* 1999; 355: 575.

Premature labour. Nimesulide has been tried as an alternative to indometacin to delay labour in a patient with a history of preterm delivery.[1] Nimesulide was given from 16 to 34 weeks of gestation and a successful delivery started 6 days after withdrawal. There appeared to be no adverse effect on fetal renal function or the ductus arteriosus. The authors suggested that fetal prostaglandin synthesis might be mainly mediated through cyclo-oxygenase-1 and that a relatively selective cyclo-oxygenase-2 inhibitor such as nimesulide might produce fewer adverse effects on the fetus than other non-selective NSAIDs. However, adverse renal effects have been reported in some neonates whose mothers received nimesulide for premature labour, see above.

1. Sawdy R, *et al.* Use of a cyclo-oxygenase type-2-selective non-steroidal anti-inflammatory agent to prevent preterm delivery. *Lancet* 1997; 350: 265–6.

Preparations

Proprietary Preparations (details are given in Part 3)
Belg.: Mesulid; ***Braz.:*** Antiflogil; Deglogen; Nisulid; Scaflam; Scalid; Sintalgin; ***Fin.:*** Nimed; ***Fr.:*** Nexen; ***Hong Kong:*** Nidol; ***Irl.:*** Aulin; Mesulid; ***Israel:*** Mesulid; ***Ital.:*** Algimesil; Algolider; Antalgo; Areuma; Aulin; Biosal; Domes; Edemax; Efridol; Eudolene; Fansidol; Fenisal; Flolid; Isodol; Laidor; Ledoren; Mesid†; Mesulid; MF 110†; Nerelid; Nide; Nidol†; Nimedex; Nimesil; Nimesulene; Nimexan; Nims; Nisal†; Noalgos; Noxalide; Remov; Resulin; Solving; Sulidamor; Sulide; Teonim; ***Mex.:*** Apolide; Eskaflam; Mesulid; Redaflam; Severin; ***Port.:*** Aulin; Donulide; Jabasulide; Nimed; Sulimed; ***Spain:*** Antifloxil; Guaxan; ***Switz.:*** Aulin; Nisulid; ***Thai.:*** Nidol.

Nonivamide (9265-t)

Nonivamide *(rINN)*.

Nonylvanillamide. *N*-Vanillylnonamide; *N*-[(4-Hydroxy-3-methoxyphenyl)methyl]nonanamide.

$C_{17}H_{27}NO_3$ = 293.4.

CAS — 2444-46-4.

NOTE. Use of the term 'synthetic capsaicin' to describe nonivamide has arisen from the use of nonivamide as an adulterant for capsaicin and capsicum oleoresin.

Profile

Nonivamide is used in topical preparations as a rubefacient.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: ABC Warme-Pflaster Sensitive; Gothaplast Capsicum-Warmepflaster.

Multi-ingredient: ***Aust.:*** Finalgon; Forapin†; Rubriment; ***Austral.:*** Finalgon; ***Belg.:*** Forapin†; ***Canad.:*** Finalgon; ***Ger.:*** ABC Warme-Salbe; Akrotherm; Finalgon; Histajodol N; Infrotto Ultra; Lomazell forte N; Ostochont; Rheuma-Liquidum; Rheumasalbe; Rubriment; Vertebralon N; ***NZ:*** Finalgon; ***Port.:*** Finalgon; ***Spain:*** Finulgon; ***Switz.:*** Forapin; Histalgane; Radalgin. Roliwol St†; Thermocutan.

The symbol † denotes a preparation no longer actively marketed

Nonsteroidal Anti-inflammatory Drugs (2600-p)

NSAIDs.

Adverse Effects and Treatment

The commonest side-effects occurring during therapy with NSAIDs are generally gastrointestinal disturbances, such as gastrointestinal discomfort, nausea, and diarrhoea; these are usually mild and reversible but in some patients peptic ulceration and severe gastrointestinal bleeding may occur. It is generally agreed that the gastrointestinal effects of NSAIDs are due to inhibition of cyclo-oxygenase-1 (COX-1); the selective inhibition of COX-2 improves gastrointestinal tolerance.

CNS-related side-effects include headache, vertigo, dizziness, nervousness, tinnitus, depression, drowsiness, and insomnia. Hypersensitivity reactions may occur occasionally and include fever, angioedema, bronchospasm, and rashes. Hepatotoxicity and aseptic meningitis, which occur rarely, may also be hypersensitivity reactions. Some patients may experience visual disturbances.

Haematological adverse effects of NSAIDs include anaemias, thrombocytopenia, neutropenia, eosinophilia, and agranulocytosis. Unlike aspirin, inhibition of platelet aggregation is reversible with other NSAIDs.

Some NSAIDs have been associated with nephrotoxicity such as interstitial nephritis and nephrotic syndrome; renal failure may be provoked by NSAIDs especially in patients with pre-existing renal impairment. Haematuria has also occurred. Fluid retention may occur, rarely precipitating heart failure in elderly patients. Long-term use or abuse of analgesics, including NSAIDs, has been associated with nephropathy. Other adverse effects include photosensitivity. Alveolitis, pulmonary eosinophilia, pancreatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis are other rare adverse effects. Induction or exacerbation of colitis has also been reported.

Further details concerning the adverse effects of the individual NSAIDs may be found under their respective monographs.

◊ The relative toxicity of NSAIDs is a continuing subject of debate.[1] Attempts have been made to rank these drugs according to their toxicity on various body systems.[2] For further details see below under individual headings.

1. Skeith KJ, *et al.* Differences in NSAID tolerability profiles: fact or fiction? *Drug Safety* 1994; 10: 183–95.
2. Committee on Safety of Medicines/Medicines Control Agency. Relative safety of oral non-aspirin NSAIDs. *Current Problems* 1994; 20: 9–11.

Effects on the blood. The UK Committee on Safety of Medicines has provided data on the reports it had received between July 1963 and January 1993 on agranulocytosis and neutropenia.[1] Several groups of drugs were commonly implicated, among them NSAIDs for which there were 133 reports of agranulocytosis (45 fatal) and 187 of neutropenia (15 fatal). The most frequently implicated NSAID was phenylbutazone with 74 reports of agranulocytosis (39 fatal) and 40 of neutropenia (4 fatal).

1. Committee on Safety of Medicines/Medicines Control Agency. Drug-induced neutropenia and agranulocytosis. *Current Problems* 1993; 19: 10–11.

Effects on the cardiovascular system. A meta-analysis[1] of 50 randomised trials studying the effects of NSAIDs on *blood pressure* in a total of 771 patients found that NSAIDs had elevated mean supine blood pressure by 5 mmHg. Piroxicam, indometacin, and ibuprofen had produced the greatest increase but the effect was only found to be statistically significant for piroxicam. Aspirin, sulindac, and flurbiprofen produced the smallest elevation in blood pressure while the effect of tiaprofenic acid, diclofenac, and naproxen was intermediate. The increase was more marked in studies in which patients had received antihypertensive therapy than in those where such treatment had not been used. NSAIDs had antagonised all antihypertensive therapy but the effect had been greater against beta blockers and vasodilators than against diuretics. An earlier meta-analysis of intervention studies had produced similar results.[2] Of the 1324 patients who had received NSAIDs, increases in mean arterial pressure were greatest in hypertensive patients who had taken either indometacin, naproxen, or piroxicam, although results were only significant for indometacin and naproxen. Sulindac and aspirin had minimal effects on mean arterial pressure.

It has been suggested that the use of NSAIDs in the elderly may increase the risk of the need for antihypertensive therapy.[3] A study[3] of 9411 patients aged 65 years or older who had just started treatment with antihypertensives found that 41% had used NSAIDs in the previous year compared with 26% of 9629 control patients not being treated with antihypertensives.

The recent use of NSAIDs has also been associated with an increased risk of developing *heart failure* in elderly patients. A case-control study[4] found that the use of an NSAID in the previous week doubled the odds of being admitted to hospital with heart failure; this risk was increased tenfold in those with a history of heart disease. The study also suggested an association between both high-dose and long drug plasma half-life and an increased risk of heart failure.

For mention of the cardiovascular effects of the selective cyclo-oxygenase-2 inhibitors including their lack of antiplatelet activity, see under Rofecoxib, p.81.

1. Johnson AG, *et al.* Do nonsteroidal anti-inflammatory drugs affect blood pressure? *Ann Intern Med* 1994; 121: 289–300.
2. Pope JE, *et al.* A meta-analysis of the effects of nonsteroidal anti-inflammatory drugs on blood pressure. *Arch Intern Med* 1993; 153: 477–84.
3. Gurwitz JH, *et al.* Initiation of antihypertensive treatment during nonsteroidal anti-inflammatory drug therapy. *JAMA* 1994; 272: 781–6.
4. Page J, Henry D. Consumption of NSAIDs and the development of congestive heart failure in elderly patients: an underrecognised public health problem. *Arch Intern Med* 2000; 160: 777–84.

Effects on the CNS. A literature review[1] revealed that headache, hearing loss, and tinnitus are the most frequent CNS adverse effects in patients taking NSAIDs. Aseptic meningitis has occurred rarely in patients using NSAIDs such as naproxen, sulindac, or tolmetin, but the most common reports are in patients with systemic lupus erythematosus who were receiving ibuprofen (see also p.43). Reports of psychosis appear to be rare and have involved indometacin or sulindac, but in the reviewers' experience it is probably under-reported and is typically seen in elderly patients given indometacin. The role of NSAIDs in the development of cognitive decline in the elderly is unclear. They have been associated with memory impairment and attention deficits in elderly patients,[1,2] especially when given in high doses;[3] however some authors have also reported that long-term NSAID use may reduce the rate of cognitive decline[3,4] or the risk of developing Alzheimer's disease.[5]

1. Hoppmann RA, *et al.* Central nervous system side effects of nonsteroidal anti-inflammatory drugs: aseptic meningitis, psychosis, and cognitive dysfunction. *Arch Intern Med* 1991; 151: 1309–13.
2. Saag KG, *et al.* Nonsteroidal antiinflammatory drugs and cognitive decline in the elderly. *J Rheumatol* 1995; 22: 2142–7.
3. Karplus TM, Saag KG. Nonsteroidal anti-inflammatory drugs and cognitive function - do they have a beneficial or deleterious effect? *Drug Safety* 1998; 19: 427–33.
4. Rozzini R, *et al.* Protective effect of chronic NSAID use on cognitive decline in older persons. *J Am Geriatr Soc* 1996; 44: 1025–9.
5. Stewart WF, *et al.* Risk of Alzheimer's disease and duration of NSAID use. *Neurology* 1997; 48: 626–32.

Effects on electrolytes. See under Effects on the Kidneys, below.

Effects on the eyes. Ocular effects such as blurred vision occur rarely in patients taking NSAIDs. Other more serious effects on the eyes associated with NSAIDs also appear to be rare. In the USA the National Registry of Drug-Induced Ocular Side Effects analysed 144 reports they received of possible adverse optic nerve reactions associated with the use of NSAIDs.[1] Of the 24 cases of papilloedema with or without pseudotumour cerebri more than half were associated with propionic acid derivatives, but it was considered that the data indicated that, on rare occasions, most NSAIDs could cause this effect; the number of reports for individual drugs was: 7 for ibuprofen, 5 each for indometacin and naproxen, 3 for meclofenamate, and 1 each for diflunisal, ketoprofen, sulindac, and tolmetin. Almost two-thirds of the 120 cases of optic or retrobulbar neuritis were also associated with propionic acid derivatives; the number of reports for individual drugs was: ibuprofen 43, naproxen 17, indometacin 9, benoxaprofen 8, phenylbutazone 8, piroxicam 8, zomepirac 7, sulindac 6, fenoprofen 5, oxyphenbutazone 3, meclofenamate 2, tolmetin 2, diflunisal 1, and ketoprofen 1.

There have been reports of severe corneal toxicity associated with the use of some topical NSAIDs, such as diclofenac and ketorolac, in the eye (see p.30).

1. Fraunfelder FT, *et al.* Possible optic nerve side effects associated with nonsteroidal anti-inflammatory drugs. *J Toxicol Cutan Ocul Toxicol* 1994; 13: 311–16.

Effects on the gastrointestinal tract. NSAIDs can cause clinically important damage of the gastrointestinal tract. The complex mechanisms involved are not fully understood, although it is generally accepted that the inhibition of cyclo-oxygenase-1 (COX-1) results in gastrointestinal toxicity and that the selective COX-2 inhibitors may be less gastrotoxic than the traditional NSAIDs (see below).[1-3] The gastric mucosa is damaged both by local and systemic effects of NSAIDs.[2] The local effect is pH-dependent and varies between individual drugs. The systemic effect is pH-independent, can occur with any route of administration, and is less drug specific. It is this effect that is thought to involve COX-1 inhibition.

NSAIDs may increase the incidence of bleeding in the upper gastrointestinal tract and of perforation, but serious complications are relatively infrequent. Although the effects of NSAIDs on the upper gastrointestinal tract are well recognised they have also been associated with damage to the distal small intestine and colon.[6-8] Risk factors continue to be studied and so far the most important patient-related factors for upper gastrointestinal toxicity are old age, a history of peptic ulcers or bleeding of the gastrointestinal tract, and concomitant use of corticosteroids. A pilot study has also suggested that NSAIDs can produce a high degree of gastrointestinal toxicity in children.[9] Whether infection with *Helicobacter pylori* affects the risk for NSAID-induced peptic ulcers is unclear.[10] Duration of therapy is not thought to influence the risk for serious events; a recent cohort study[11] has found that the risk of gastrointestinal bleeding or perforation with NSAIDs is constant throughout treatment.

Several studies[12-14] have been conducted on the relative toxicity of oral NSAIDs on the upper gastrointestinal tract and various rankings of these drugs have been discussed.[15-17] The UK Committee on Safety of Medicines (CSM)[17] examined 10 epidemiological studies for 7 oral non-aspirin NSAIDs and also examined the spontaneous reports they had received of gastrointestinal effects associated with NSAIDs. The CSM concluded that **azapropazone** was associated with the *highest* risk of gastrointestinal reactions and **ibuprofen** with the *lowest* risk. **Piroxicam, ketoprofen, indometacin, naproxen,** and **diclofenac** had an *intermediate* risk; it was considered that the risk for piroxicam might be higher than for the other NSAIDs with intermediate toxicity. In a systematic review[18] of controlled epidemiological studies that found a relation between NSAID use and hospital admission for gastric haemorrhage or perforation, the low risk of serious gastric toxicity with ibuprofen appeared to be attributable mainly to the low doses used clinically; higher doses of ibuprofen were associated with a similar risk to indometacin and naproxen. For reference to an association between aspirin and the most severe gastric lesions compared with other NSAIDs, see p.15. Results from controlled trials have confirmed that the selective COX-2 inhibitors are associated with a lower incidence of serious gastrointestinal effects, such as bleeding, perforation, and obstruction, than the traditional NSAIDs[19] (see also Celecoxib, p.24 and Rofecoxib, p.81 for further details). However, since the risk of such effects is inherently low in those with no history of peptic ulcer disease, the general prescribing of selective COX-2 inhibitors to all patients requiring an NSAID is questioned. Indeed, in the UK, the use of selective COX-2 inhibitors is limited to those at high risk of developing serious gastrointestinal problems if given a non-selective NSAID. High-risk patients include the elderly, those already receiving gastrotoxic drugs, and those with existing gastrointestinal disorders

There has been concern that topical use of NSAIDs may also be associated with gastrointestinal toxicity but a case-controlled study[20] concluded that topical administration was not associated with significant upper gastrointestinal bleeding or perforation.

Apart from the selection of an NSAID with a lower risk for gastrointestinal toxicity, other methods used for the prevention or treatment of NSAID-associated ulceration are discussed under the treatment of peptic ulcer disease on p.1208.

1. Hayllar J, Bjarnason I. NSAIDs, Cox-2 inhibitors, and the gut. *Lancet* 1995; **346:** 521–2.
2. Bjorkman DJ. Nonsteroidal anti-inflammatory drug-induced gastrointestinal injury. *Am J Med* 1996; **101** (suppl 1A): 25S–32S
3. Soll A. Pathogenesis of nonsteroidal anti-inflammatory drug-related upper gastrointestinal toxicity. *Am J Med* 1996; **105** (suppl 5A): 10S–16S.
4. Hawkey CJ. COX-2 inhibitors *Lancet* 1999; 353: 307–14 Correction. *ibid.* 1440. [dose]
5. Wolfe MM, *et al.* Gastrointestinal toxicity of nonsteroidal antiinflammatory drugs. *N Engl J Med* 1999; **340:** 1888–99
6. Kwo PY, Tremaine WJ. Nonsteroidal anti-inflammatory drug-induced enteropathy: case discussion and review of the literature. *Mayo Clin Proc* 1995; **70:** 55–61.
7. Gleeson MH, *et al.* Non-steroidal anti-inflammatory drugs, salicylates, and colitis. *Lancet* 1996; **347:** 904–5.
8. Evans JMM, *et al.* Non-steroidal anti-inflammatory drugs are associated with emergency admission to hospital for colitis due to inflammatory bowel disease. *Gut* 1997; **40:** 619–22.
9. Mulberg AE, *et al.* Identification of nonsteroidal antiinflammatory drug-induced gastroduodenal injury in children with juvenile rheumatoid arthritis. *J Pediatr* 1993; **122:** 647–9.
10. Marshall B. NSAIDs and Helicobacter pylori: therapeutic options. *Lancet* 1998; **352:** 1001–3
11. MacDonald TM, *et al.* Association of upper gastrointestinal toxicity of non-steroidal anti-inflammatory drugs with continued exposure: cohort study. *BMJ* 1997; **315:** 1333–7
12. Kaufman DW, *et al.* Nonsteroidal anti-inflammatory drug use in relation to major upper gastrointestinal bleeding. *Clin Pharmacol Ther* 1993; **53:** 485–94
13. García Rodríguez LA, Jick H. Risk of upper gastrointestinal bleeding and perforation associated with individual non-steroidal anti-inflammatory drugs. *Lancet* 1994; **343:** 769–72.
14. Langman MJS, *et al.* Risks of bleeding peptic ulcer associated with individual non-steroidal anti-inflammatory drugs. *Lancet* 1994; **343:** 1075–8.
15. Bateman DN. NSAIDs: time to re-evaluate gut toxicity. *Lancet* 1994; **343:** 1051–2.
16. Smith CC, *et al.* NSAIDs and gut toxicity. *Lancet* 1994; **344:** 56–7.
17. Committee on Safety of Medicines/Medicines Control Agency. Relative safety of oral non-aspirin NSAIDs. *Current Problems* 1994; **20:** 9–11
18. Henry D, *et al.* Variability in risk of gastrointestinal complications with individual non-steroidal anti-inflammatory drugs: results of a collaborative meta-analysis. *BMJ* 1996; **312:** 1563–6.
19. Fitzgerald GA, Patrono C. The coxibs, selective inhibitors of cyclooxygenase-2. *N Engl J Med* 2001; **345:** 433–42.
20. Evans JMM, *et al.* Topical non-steroidal anti-inflammatory drugs and admission to hospital for upper gastrointestinal bleeding and perforation: a record linkage case-control study. *BMJ* 1995; **311:** 22–6.

Effects on the joints. There is concern that NSAIDs such as indometacin may accelerate the rate of cartilage destruction in patients with osteoarthritis.[1,2]

1. Rashad S, *et al.* Effect of non-steroidal anti-inflammatory drugs on the course of osteoarthritis. *Lancet* 1989; **ii:** 519–22.
2. Huskisson EC, *et al.* Effects of antiinflammatory drugs on the progression of osteoarthritis of the knee. *J Rheumatol* 1995; **22:** 1941–6.

Effects on the kidneys. NSAIDs can produce a number of different renal disorders following systemic or topical administration,[1] some of which are due to their inhibition of prostaglandin synthesis.[2,3] Under normal conditions prostaglandins appear to have little effect on renal homoeostasis but in the presence of renal vasoconstriction their vasodilator action increases renal blood flow and thereby helps to maintain renal function.[4,5] Patients whose renal function is being maintained by prostaglandins are therefore at risk from NSAIDs. Such patients include those with impaired circulation, the elderly, those on diuretics, and those with heart failure or renal vascular disease.[2,4] Other risk factors for renal impairment with NSAIDs include dehydration, cirrhosis, surgery, sepsis,[6] and a history of gout or hyperuricaemia.[6,7] The half-life of an NSAID may be a more important determinant of the risk of developing functional renal impairment than the ingested dose.[7] Evidence of renal toxicity of the cyclo-oxygenase-2 (COX-2) selective inhibitors is less extensive; however such NSAIDS appear to have effects on renal function similar to those of the non-selective NSAIDs.[8]

ACE inhibitors can also produce renal impairment and combined use with NSAIDs should be undertaken with great care. Prostaglandin inhibition may also lead to salt and water retention particularly when there is pre-existing hypertension or sodium depletion.[4] NSAIDs, therefore, tend to counteract the action of diuretics and antihypertensives.[2,4] There have been isolated reports of severe hyponatraemia and other symptoms resembling the syndrome of inappropriate antidiuretic hormone secretion in patients taking NSAIDs.[9,10]

Potassium homoeostasis is less dependent on prostaglandins and hyperkalaemia occurs infrequently with NSAIDs.[3] It is more likely to occur in patients with specific risk factors such as those receiving potassium supplements or potassium-sparing diuretics.[3] Indometacin appears to be the main NSAID implicated (see also Effects on Electrolytes, p.45).

NSAIDs may cause acute interstitial nephritis, perhaps involving an allergic response,[2,3,11] and it may progress to interstitial fibrosis or papillary necrosis.[3,12]

Analgesic abuse or prolonged excessive use can produce nephropathy, a condition characterised by renal papillary necrosis and chronic interstitial nephritis, and, eventually, renal failure.[13] Phenacetin, a para-aminophenol derivative, has long been recognised as being one of the main drugs responsible for analgesic nephropathy,[14,15] but nephropathy has also been associated with the long-term use of NSAIDs and paracetamol without phenacetin.[16]

1. O'Callaghan CA, *et al.* Renal disease and use of topical non-steroidal anti-inflammatory drugs. *BMJ* 1994; **308:** 110–11
2. Kendall MJ, Horton RC. Clinical pharmacology and therapeutics. *Postgrad Med J* 1990; **66:** 166–85
3. Whelton A, Hamilton CW. Nonsteroidal anti-inflammatory drugs: effects on kidney function. *J Clin Pharmacol* 1991; **31:** 588–98.
4. Harris K. The role of prostaglandins in the control of renal function. *Br J Anaesth* 1992; **69:** 233–5.
5. Kenny GNC. Potential renal, haematological and allergic adverse effects associated with nonsteroidal anti-inflammatory drugs. *Drugs* 1992; **44** (suppl 5): 31–7
6. MacDonald TM. Selected side-effects: 14. non-steroidal anti-inflammatory drugs and renal damage. *Prescribers' J* 1994; **34:** 77–80.
7. Henry D, *et al.* Consumption of non-steroidal anti-inflammatory drugs and the development of functional renal impairment in elderly subjects: results of a case-control study. *Br J Clin Pharmacol* 1997; **44:** 85–90.
8. Perazella MA, Tray K. Selective cyclooxygenase-2 inhibitors: a pattern of nephrotoxicity similar to traditional nonsteroidal antiinflammatory drugs. *Am J Med* 2001; **111:** 64–7.
9. Petersson I, *et al.* Water intoxication associated with non-steroidal anti-inflammatory drug therapy. *Acta Med Scand* 1987; **221:** 221–3.
10. Cheung NT, *et al.* Syndrome of inappropriate secretion of antidiuretic hormone induced by diclofenac. *BMJ* 1993; **306:** 186.
11. Ravnskov U. Glomerular, tubular and interstitial nephritis associated with non-steroidal antiinflammatory drugs. Evidence of a common mechanism. *Br J Clin Pharmacol* 1999; **47:** 203–10.
12. Sandler DP, *et al.* Nonsteroidal anti-inflammatory drugs and the risk for chronic renal disease. *Ann Intern Med* 1991; **115:** 165–72.
13. De Broe ME, Elseviers MM. Analgesic nephropathy. *N Engl J Med* 1998; **338:** 446–52.
14. Sandler DP, *et al.* Analgesic use and chronic renal disease. *N Engl J Med* 1989; **320:** 1238–43.
15. Dubach UC, *et al.* An epidemiologic study of abuse of analgesic drugs: effects of phenacetin and salicylate on mortality and cardiovascular morbidity 1968 to 1987. *N Engl J Med* 1991; **324:** 155–60.
16. Perneger TV, *et al.* Risk of kidney failure associated with the use of acetaminophen, aspirin, and nonsteroidal antiinflammatory drugs. *N Engl J Med* 1994; **331:** 1675–9.

Effects on the liver. A retrospective study involving over 220 000 adults who were either using, or had used, NSAIDs identified a small excess risk of serious, acute non-infectious liver injury; in current users there was a twofold increase in risk and there was a predominance of the cholestatic type of liver injury among such patients. Nonetheless, admissions to hospital for liver injury had been rare.[1] In a review[2] of cohort and case-control studies describing an association between NSAIDs and liver disease, the strongest evidence emerged for sulindac. There were also a significant number of reports of hepatotoxicity on rechallenge with diclofenac. Evidence of hepatotoxicity for other NSAIDs was weak, although the risk appeared to be high when they were used with other hepatotoxic drugs. However, the overall incidence of liver disease with NSAIDs was very low.

1. García Rodríguez LA, *et al.* The role of non-steroidal anti-inflammatory drugs in acute liver injury. *BMJ* 1992; **305:** 865–8. Correction. *ibid.*: 920.
2. Manoukian AV, Carson JL. Nonsteroidal anti-inflammatory drug-induced hepatic disorders. *Drug Safety* 1996; **15:** 64–71.

Effects on the lungs. Adverse pulmonary effects such as pneumonitis, alveolitis, pulmonary infiltrates, and pulmonary fibrosis, often suggestive of an allergic or immune reaction, have been reported with a number of NSAIDs. For references, see under individual monographs.

Effects on the pancreas. A review[1] of drug-induced pancreatitis considered that sulindac was amongst the drugs for which a definite association with pancreatitis had been established. There had been isolated reports of pancreatitis with ketoprofen, mefenamic acid, and piroxicam but any association was considered to be questionable. For further references see under individual monographs.

1. Underwood TW, Frye CB. Drug-induced pancreatitis. *Clin Pharm* 1993; **12:** 440–8.

Effects on the skin. The diverse cutaneous reactions to NSAIDs have been reviewed.[1] Of 250 children attending a rheumatology clinic 34 (13.6%) were found to have 4 or more facial scars of unknown origin.[2] This number of scars was found in 22.2% of the 116 children who had received naproxen and in 9.2% of the 87 who had received other NSAIDs. Children affected were more likely to have light skin and blue or green eyes. It was not known whether this was a form of phototoxic reaction but pseudoporphyria-like eruptions associated with NSAIDs, and naproxen in particular (see p.61), have been reported.

See also under Hypersensitivity, below.

1. Bigby M, Stern R. Cutaneous reactions to nonsteroidal anti-inflammatory drugs. *J Am Acad Dermatol* 1985; **12:** 866–76.
2. Wallace CA, *et al.* Increased risk of facial scars in children taking nonsteroidal antiinflammatory drugs. *J Pediatr* 1994; **125:** 819–22.

Hypersensitivity. NSAIDs have produced a wide range of hypersensitivity reactions in susceptible individuals; the most common include skin rashes, urticaria, rhinitis, angioedema, bronchoconstriction, and anaphylactic shock. Hypersensitivity to NSAIDs appears to occur more frequently in patients with asthma or allergic disorders but other risk factors have been identified (for further details see under Aspirin, p.15). The occurrence of aspirin sensitivity in patients with asthma and nasal polyps has been referred to as the 'aspirin triad'. There is considerable cross-reactivity between aspirin and other NSAIDs and it is generally recommended that patients who have had a hypersensitivity reaction to aspirin or any other NSAID should avoid all NSAIDs. For references to hypersensitivity reactions associated with NSAIDs, see under individual monographs.

Overdosage. The clinical signs and symptoms following acute overdosage of NSAIDs and methods of treatment have been reviewed.[1] In general, symptoms of NSAID poisoning are mild, and usually include nausea and vomiting, headache, drowsiness, blurred vision, and dizziness. There have been isolated case reports of more serious toxicity, including seizures, hypotension, apnoea, coma, and renal failure, although usually after ingestion of substantial quantities. Seizures are a particular problem with mefenamic acid overdosage.

Treatment of NSAID overdosage is entirely supportive. Gastric lavage and activated charcoal may be of benefit within 1 hour of ingestion. Multiple doses of activated charcoal may be useful in enhancing elimination of NSAIDs with long half-lives such as piroxicam and sulindac. Forced diuresis, haemodialysis, or haemoperfusion are unlikely to be of benefit for NSAID overdosage, although haemodialysis may be required if oliguric renal failure develops.

1. Smolinske SC, *et al.* Toxic effects of nonsteroidal anti-inflammatory drugs in overdose: an overview of recent evidence on clinical effects and dose-response relationships. *Drug Safety* 1990; **5:** 252–74

Precautions

NSAIDs should not be given to patients with peptic ulceration and should be used with caution, if at all, in patients with a history of such disorders. To reduce the risk of gastrointestinal effects, NSAIDs may be taken with or after food or milk. Histamine H_2-antagonists, omeprazole, or misoprostol may be used for a similar purpose in high-risk patients (see under Peptic Ulcer Disease, p.1208). However, food, milk, and

such measures may reduce the rate and extent of drug absorption. UK authorities recommend that NSAIDs associated with the lowest risk of gastrointestinal toxicity (see Effects on the Gastrointestinal Tract, under Adverse Effects, above) should be tried first in the lowest recommended dose, and not more than one oral NSAID should be used at a time; selective inhibitors of cyclo-oxygenase-2 (COX-2) are reserved for patients at highest risk.

NSAIDs should be used with caution in patients with infections, since symptoms such as fever and inflammation may be masked, and also used with caution in patients with asthma or allergic disorders. NSAIDs (including topical NSAIDs) are contra-indicated in patients with a history of hypersensitivity reactions to such drugs, including those in whom attacks of asthma, angioedema, urticaria, or rhinitis have been precipitated by aspirin or any other NSAID.

Other general precautions to be observed include administration to patients with haemorrhagic disorders, hypertension, and impaired renal, hepatic, or cardiac function. Patients undergoing therapy with some NSAIDs may need to be monitored for the development of blood, kidney, liver, or eye disorders. NSAIDs should be used with caution in the elderly and may need to be given in reduced doses.

Regular use of NSAIDs during the third trimester of pregnancy may result in closure of fetal ductus arteriosus *in utero*, and possibly in persistent pulmonary hypertension of the newborn. The onset of labour may be delayed and its duration increased.

Some NSAIDs can interfere with thyroid function tests by lowering serum-thyroid hormone concentrations.

Further details concerning the precautions of the individual NSAIDs may be found under their respective monographs.

Pregnancy. Results from a case-control interview study[1] suggested that prenatal ingestion of aspirin or other NSAIDs might be implicated in persistent pulmonary hypertension of the newborn. The authors suggested that these drugs may be responsible for gestational structural or functional alterations of the pulmonary vasculature. However, the primary cause might also have been the underlying disorder for which the NSAIDs or aspirin were ingested. They were unable to pinpoint in which trimester the drugs might have their proposed action, and concluded that further evaluation was necessary. A more recent study[2] has found that persistent pulmonary hypertension of the newborn is significantly associated with *in utero* NSAID exposure, particularly to aspirin, ibuprofen, and naproxen. Fetal exposure to an NSAID was confirmed by meconium analysis.

Another study[3] has suggested that the risk of miscarriage is increased with NSAID use; however, the authors pointed out that the observation remained to be confirmed. The same study also found no association between NSAID use and congenital abnormalities, low birth weight, or preterm birth.

Most manufacturers recommend avoidance of NSAIDs during pregnancy, unless the proposed benefit outweighs the risks, but in many cases published data on use of the drugs in pregnancy is scanty or absent, making an informed decision difficult.

1. Van Marter LJ, *et al.* Persistent pulmonary hypertension of the newborn and smoking and aspirin and nonsteroidal antiinflammatory drug consumption during pregnancy. *Pediatrics* 1996; 97: 658–63.
2. Alano MA, *et al.* Analysis of nonsteroidal antiinflammatory drugs in meconium and its relation to persistent pulmonary hypertension of the newborn. *Pediatrics* 2001; 107: 519–23.
3. Nielsen GL, *et al.* Risk of adverse birth outcome and miscarriage in pregnant users of non-steroidal anti-inflammatory drugs: population based observational study and case-control study. *BMJ* 2001; 322: 266–70.

Renal impairment. The *British National Formulary* recommends that NSAIDs in general should be given at the lowest effective dose in patients with mild renal impairment and that renal function should be carefully monitored; they should be avoided if possible in patients with moderate to severe renal impairment.

See also under individual monographs.

Thyroid function tests. References to the interference with thyroid function tests by some NSAIDs.

1. Bishnoi A, *et al.* Effect of commonly prescribed nonsteroidal anti-inflammatory drugs on thyroid hormone measurements. *Am J Med* 1994; 96: 235–8.

Interactions

Notable interactions involving NSAIDs include enhancement of the effects of oral anticoagulants (especially by azapropazone and phenylbutazone) and increased plasma concentrations of lithium, methotrexate, and cardiac glycosides. The risk of nephrotoxicity may be increased if given with ACE inhibitors, ciclosporin, tacrolimus, or diuretics. Effects on renal function may lead to reduced excretion of some drugs. There may also be an increased risk of hyperkalaemia with ACE inhibitors and potassium-sparing diuretics. The antihypertensive effects of some antihypertensives including ACE inhibitors, beta blockers, and diuretics may be reduced. Convulsions may occur due to an interaction with quinolones. NSAIDs may enhance the effects of phenytoin and sulfonylurea antidiabetics. The effects of NSAIDs might be enhanced by use with moclobemide. The concomitant use of more than one NSAID (including aspirin) should be avoided because of the increased risk of adverse effects. The risk of gastrointestinal bleeding and ulceration associated with NSAIDs is increased when used with corticosteroids, the antiplatelets clopidogrel and ticlopidine, or, possibly, alcohol, bisphosphonates, or oxpentifylline [pentoxifylline]. There may be an increased risk of haematotoxicity during concomitant use of zidovudine and NSAIDs; blood counts 1 to 2 weeks after starting use together are recommended. Ritonavir may increase the plasma concentrations of NSAIDs. The manufacturer of mifepristone advises that NSAIDs or aspirin should be avoided for 8 to 12 days after mifepristone use because of a theoretical risk that these prostaglandin synthetase inhibitors may alter the efficacy of mifepristone. There have been occasional reports of increased adverse effects when NSAIDs were given with misoprostol although such combinations have sometimes been employed to *decrease* the gastrointestinal toxicity of NSAIDs.

Further details concerning the interactions of the individual NSAIDs may be found under their respective monographs.

◊ References.

1. Brouwers JRBJ, de Smet PAGM. Pharmacokinetic-pharmacodynamic drug interactions with nonsteroidal anti-inflammatory drugs. *Clin Pharmacokinet* 1994; 27: 462–85.

Antihypertensives. For reference to the relative effects of NSAIDs in antagonising different types of antihypertensive drugs, see Effects on the Cardiovascular System under Adverse Effects, above.

Pharmacokinetics

Details of the pharmacokinetics of individual NSAIDs may be found under their respective monographs.

◊ General reviews.

1. Woodhouse KW, Wynne H. The pharmacokinetics of non-steroidal anti-inflammatory drugs in the elderly. *Clin Pharmacokinet* 1987; 12: 111–22.
2. Walson PD, Mortensen ME. Pharmacokinetics of common analgesics, anti-inflammatories and antipyretics in children. *Clin Pharmacokinet* 1989; 17 (suppl 1): 116–37.
3. Simkin PA, *et al.* Articular pharmacokinetics of protein-bound antirheumatic agents. *Clin Pharmacokinet* 1993; 25: 342–50.
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Uses and Administration

Administered as single doses or in short-term intermittent therapy NSAIDs can relieve mild to moderate pain. However, it may take up to 3 weeks of use before their anti-inflammatory effects become evident. The combined analgesic and anti-inflammatory effects make them particularly useful for the symptomatic relief of painful and/or inflammatory conditions including rheumatic disorders such as rheumatoid arthritis, osteoarthritis, and the spondyloarthropathies, and also in peri-articular disorders, and soft-tissue rheumatism. Some NSAIDs are used in the management of postoperative pain. Some NSAIDs, but not aspirin or other salicylates, are also used to treat acute gouty arthritis.

Generally, it is felt that there are only small differences in anti-inflammatory activity between the various NSAIDs and choice is largely empirical. Responses of individual patients vary widely. Thus, if a patient fails to respond to one NSAID, another drug may be successful. However, it has been recommended that NSAIDs associated with a low risk of gastrointestinal toxicity should generally be preferred and the lowest effective dose used. Treatment with NSAIDs such as celecoxib and rofecoxib that are selective inhibitors of cyclo-oxygenase-2 is limited in the UK to those patients considered to be at high risk of developing serious gastrointestinal problems if given a non-selective NSAID (see Effects on the Gastrointestinal Tract, above).

NSAIDs are usually given by mouth, with or after food, although some such as diclofenac, ketoprofen, ketorolac, piroxicam, and tenoxicam can be given by intramuscular injection; diclofenac, ketorolac, and tenoxicam can also be given intravenously. Some NSAIDs are applied topically or given rectally as suppositories.

Several NSAIDs are used in ophthalmic preparations for the inhibition of intra-operative miosis, control of postoperative ocular inflammation, and prevention of cystoid macular oedema.

Action. Cyclo-oxygenases play an important role in the biosynthesis of prostaglandins (p.1438). NSAIDs inhibit cyclo-oxygenase-1 (COX-1) and cyclo-oxygenase-2 (COX-2) and it is thought that inhibition of COX-1 is associated with adverse gastrointestinal effects while inhibition of COX-2 is associated with anti-inflammatory activity,[1-4] hence the interest[3] in preferential or selective inhibitors of COX-2. COX-2 inhibitors may also have a potential use in other diseases in which COX-2 might be implicated.[4] Meloxicam and nimesulide are preferential inhibitors of COX-2, that is they have a higher selectivity for COX-2 than COX-1 but are not exclusive COX-2 inhibitors; etodolac and nabumetone are also claimed to have preference for COX-2 although there is less evidence for this. Drugs with a very high selectivity for COX-2 have also been developed. Celecoxib and rofecoxib are two examples. Although the selective inhibition of COX-2 may be associated with reduced gastrointestinal toxicity, adverse effects associated with such inhibition have been noted in other body systems, see Effects on the Cardiovascular System and Effects on the Kidneys, above.

There is evidence that NSAIDs may also have a central mechanism of action that augments the peripheral mechanism.[6]

Many NSAIDs possess centres of chirality within their molecular structure, with different chiral forms (enantiomers) having different degrees of pharmacological activity.[8,9] For example, indometacin, its analogues, and some arylpropionic acids are chiral drugs with the S(+)-enantiomer in most cases showing the dominant pharmacological activity. However, the ratio of S/R activity varies between drugs and between animal species. NSAIDs are generally administered clinically as the racemate with only a few currently being given as the (S)-enantiomer (for example, dexketoprofen). The chirality of a drug may have subtle effects on its toxicity and interactions, and it may be more desirable to administer a drug as its active enantiomer.[9]

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Colic pain. Prostaglandins have been implicated in the aetiology of biliary colic (p.5), and some NSAIDs such as diclofenac, indometacin, and ketoprofen have been used to relieve such pain.

Ectopic ossification. NSAIDs are an effective alternative to radiotherapy for prevention of ectopic ossification (p.744) after surgery or trauma. Indometacin is widely used for this purpose.

References.

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Eye disorders. Miosis resistant to conventional mydriatics often develops during ocular surgery, possibly due to release of prostaglandins and other substances associated with trauma. NSAIDs, which are prostaglandin synthetase inhibitors, are therefore used prophylactically as eye drops before ocular surgery to ameliorate intra-operative miosis but there has been some doubt that the effect they produce is of clinical significance. Those commonly used include diclofenac, indometacin, flurbiprofen, and suprofen. These drugs do not possess intrinsic mydriatic properties.

Some NSAIDs are used topically or systemically in a number of inflammatory ocular disorders, including inflammation and cystoid macular oedema following ocular surgery (see below). However, their role in the treatment of macular oedema associated with uveitis (p.1060) is less clear. NSAIDs are also used in the treatment of scleritis (see p.1058).

References.

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POSTOPERATIVE INFLAMMATORY OCULAR DISORDERS Corticosteroids are used topically for the control of **postoperative ocular inflammation** but caution is required as they can delay wound healing and mask postoperative infection. They should only be used for short periods as they can cause glaucoma in susceptible individuals. Topical NSAIDs have also been tried. Despite some doubts over efficacy several studies have found eye drops containing diclofenac sodium to be effective in controlling signs of inflammation after ocular surgery,[1-3] but there has been some concern about reports of corneal toxicity (see p.30).

Cystoid macular oedema may follow cataract or retinal detachment surgery due to a disturbance of the blood-retinal barrier. A number of NSAIDs,[3-6] including diclofenac, flurbiprofen, indometacin, and ketorolac are used topically with or without corticosteroids to prevent or relieve cystoid macular oedema. NSAIDs such as indometacin are also used systemically in its management.

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2. Wright M, *et al.* Comparison of the efficacy of diclofenac and betamethasone following strabismus surgery. *Br J Ophthalmol* 1997; **81**: 299–301.
3. Italian Diclofenac Study Group. Efficacy of diclofenac eyedrops in preventing postoperative inflammation and long-term cystoid macular edema. *J Cataract Refract Surg* 1997; **23**: 1183–9.
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Fever. Paracetamol, salicylates and some other NSAIDs are the main antipyretics used to control fever (p.8). Paracetamol is usually the antipyretic of choice in infants and children but ibuprofen appears to be an effective alternative; salicylates are generally contra-indicated in these patients because of the possible link between their use and the development of Reye's syndrome (see under Adverse Effects of Aspirin, p.15).

Gout. NSAIDs are the drugs usually used first for the treatment of acute attacks of gout (p.397). Since the treatment of chronic gout can lead to the mobilisation of urate crystals from established tophi to produce acute attacks, NSAIDs may also be used for the prophylaxis of acute gout during the first few months of antihyperuricaemic therapy.

Headache. An NSAID is often tried first for the symptomatic treatment of various types of headache including migraine (p.449) and tension-type headache (p.450). NSAIDs may also be effective prophylactic drugs for migraine, although propranolol or pizotifen are generally preferred. Chronic paroxysmal hemicrania, a rare variant of cluster headache (p.449), responds to indometacin.

Kidney disorders. Although NSAIDs can produce adverse effects on the kidney (see above) they may have a role in the management of some types of glomerular kidney disease (p.1051). They may be of use for the control of proteinuria due to nephrotic syndrome except when there is overt renal failure.

Malignant neoplasms. Results of a study by the American Cancer Society[1] have suggested that regular use of aspirin may reduce the risk of developing fatal cancer of the oesophagus, stomach, colon, or rectum. Death rates due to other gastrointestinal cancers did not appear to be affected. Other studies[2-7] appear to support the reduced risk of colorectal cancer (p.493) in regular users of aspirin or other NSAIDs. However, a 1998 study[8] found no evidence of an association between the use of aspirin and the incidence of colorectal cancer, although the authors suggest that these results may be explained by the short treatment period and the low dose of aspirin used. Long-term use of aspirin may itself be associated with an increased risk of certain other diseases.

Treatment with sulindac (p.86) has been found to reduce the number of polyps in patients with familial adenomatous polyposis, a condition which predisposes to development of colorectal cancer. Celecoxib is now indicated for use in such patients.

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Menstrual disorders. Menorrhagia (p.1490) is thought to be associated with abnormalities of prostaglandin production. Treatment with NSAIDs such as ibuprofen, mefenamic acid, or naproxen during menstruation, can reduce uterine blood loss by an average of 30% in women with menorrhagia. There does not appear to be any evidence that one NSAID is more effective than another.

NSAIDs are usually the first choice for the pain of dysmenorrhoea (p.6). Mefenamic acid may have a theoretical advantage over other NSAIDs in being able to inhibit both the synthesis and the peripheral action of prostaglandins, but clinical studies have not shown fenemates to be more effective, and systematic review has suggested that ibuprofen may have the best risk/benefit ratio.

Migraine. See under Headache, above.

Orthostatic hypotension. Fludrocortisone is usually the first drug tried in the treatment of orthostatic hypotension (p.1070) when nonpharmacological treatment has failed. NSAIDs such as flurbiprofen, ibuprofen, or indometacin may be used alone or added to treatment if the response is inadequate.

Pain. NSAIDs have a similar analgesic effect to aspirin and paracetamol in single doses but, in regular full dosage, they have both a lasting analgesic and an anti-inflammatory effect. They are used in the management of mild to moderate pain (p.2) and are of particular value in pain due to inflammation. NSAIDs may be of benefit for inflammatory pain in infants and children (p.3), although paracetamol is generally the preferred non-opioid analgesic in this age group. NSAIDs may be used in the treatment of acute low back pain (p.6) if paracetamol fails to provide adequate pain relief. NSAIDs may also be used as an adjunct to opioids in the management of severe pain such as cancer pain (p.5) and are particularly effective in bone pain of malignant origin. NSAIDs may be used for postoperative analgesia (p.4), and are of particular value following day-case surgery because of their lack of sedative effects. They are not usually considered to be strong enough as the sole analgesic following major surgery, but may be used with stronger analgesics and may allow dosage reduction of concomitant opioids. The pain of mild sickle-cell crises (p.7) may be controlled by analgesics such as NSAIDs or less potent opioids, for example codeine or dihydrocodeine. NSAIDs may be used with more potent opioids such as morphine for severe crises.

Dependence and tolerance are not a problem with non-opioid analgesics such as NSAIDs, but there is a ceiling of efficacy, above which, increasing the dose has no further therapeutic effect.

Rheumatic disorders. NSAIDs provide symptomatic relief for rheumatic disorders such as rheumatoid arthritis (p.9) and spondyloarthropathies (p.10), but they do not alter the course of the disease and additional antirheumatic drugs may need to be given to prevent irreversible joint damage. NSAIDs may also be used as an alternative to paracetamol for osteoarthritis (p.9). Short-term use of oral NSAIDs may help to relieve pain and reduce inflammation of soft-tissue rheumatism (p.10); topical formulations of some NSAIDs are also used but their therapeutic role, if any, is unclear.

Opioid Analgesics (6200-n)

Dependence and Withdrawal

Repeated administration of opioids is associated with the development of psychological and physical dependence. Although this is less of a problem with legitimate therapeutic use, dependence may develop rapidly when opioids are regularly abused for their euphoriant effects. Drug dependence of the opioid type is characterised by an overwhelming need to keep taking the drug (or one with similar properties), by a physical requirement for the drug in order to avoid withdrawal symptoms, and by a tendency to increase the dose owing to the development of tolerance.

Abrupt withdrawal of opioids from persons physically dependent on them precipitates a withdrawal syndrome, the severity of which depends on the individual, the drug used, the size and frequency of the dose, and the duration of drug use. Withdrawal symptoms may also follow the administration of an opioid antagonist such as naloxone or a mixed agonist and antagonist such as pentazocine to opioid-dependent persons. Neonatal abstinence syndrome may occur in the offspring of opioid-dependent mothers and these infants can suffer withdrawal symptoms at birth.

Opioid analgesics can be classified according to the receptors at which they act (see under Uses and Administration, below) and withdrawal syndromes are characteristic for a receptor type. Cross-tolerance and cross-dependence can be expected between opioids acting at the same receptors. Dependence associated with morphine and closely related μ-agonists appears to result in more severe withdrawal symptoms than that associated with κ-receptor agonists. Onset and duration of withdrawal symptoms also vary according to the duration of action of the specific drug. With morphine and diamorphine *withdrawal symptoms* usually begin within a few hours, reach a peak within 36 to 72 hours, and then gradually subside; they develop more slowly with methadone. Withdrawal symptoms include yawning, mydriasis, lachrymation, rhinorrhoea, sneezing, muscle tremor, weakness, sweating, anxiety, irritability, disturbed sleep or insomnia, restlessness, anorexia, nausea, vomiting, loss of weight, diarrhoea, dehydration, leucocytosis, bone pain, abdominal and muscle cramps, gooseflesh, vasomotor disturbances, and increases in heart rate, respiratory rate, blood pressure, and temperature. Some physiological values may not return to normal for several months following the acute withdrawal syndrome.

Withdrawal symptoms may be terminated by a suitable dose of the original or a related opioid. Tolerance diminishes rapidly after withdrawal so that a previously tolerated dose may prove fatal.

For a discussion of the treatment of opioid dependence and neonatal abstinence syndrome, see below.

◊ Review.

1. Van Ree JM, *et al.* Opioids, reward and addiction: an encounter of biology, psychology, and medicine. *Pharmacol Rev* 1999; **51**: 341–96.

Diagnosis. Naloxone (p.1015) and other opioid antagonists have been used to diagnose opioid dependence.

Treatment of opioid dependence. The treatment of opioid dependence has been the subject of a number of reviews and discussions.[1-7]

Planned withdrawal (**detoxification**) may be effected slowly or rapidly. The usual method in many countries is to replace the drug of dependence with *methadone* given as a liquid oral preparation, and then gradually withdraw the methadone if possible. Methadone is suitable for withdrawal therapy because it can be given orally and its long half-life allows once daily administration. Oral *diamorphine* has been used similarly to methadone: reefers containing diamorphine have also been used in some centres. *Dihydrocodeine* tablets have been used successfully. *Buprenorphine* given sublingually is another alternative to methadone in the treatment of opioid dependence. The methadone derivative *levacetylmethadol* was a more recent introduction but its proarrhythmic effects have led to its use being suspended or severely restricted.

Iatrogenic opioid dependence may occur in patients receiving μ-agonists such as morphine, fentanyl, or pethidine for the